

PCT INTERNATIONAL COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 03 January 2001 (03.01.01)	
International application No. PCT/US00/04548	Applicant's or agent's file reference WST88PCT
International filing date (day/month/year) 23 February 2000 (23.02.00)	Priority date (day/month/year) 24 February 1999 (24.02.99)
Applicant SANTOLI, Daniela et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

20 September 2000 (20.09.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
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PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : C12N 5/00, 5/02	A1	(11) International Publication Number: WO 00/50569 (43) International Publication Date: 31 August 2000 (31.08.00)
(21) International Application Number: PCT/US00/04548 (22) International Filing Date: 23 February 2000 (23.02.00) (30) Priority Data: 60/121,482 24 February 1999 (24.02.99) US (71) Applicant (for all designated States except US): THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY [US/US]; 3601 Spruce Street, Philadelphia, PA 19104-4268 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): SANTOLI, Daniela [US/US]; 933 Wootton Road, Bryn Mawr, PA 19010 (US). ROVERA, Giovanni [US/US]; 933 Wootton Road, Bryn Mawr, PA 19010 (US). CESANO, Alessandra [IT/US]; 226 W. Rittenhouse Square, The Dorchester #413, Philadelphia, PA 19103 (US). (74) Agents: BAK, Mary, E. et al.; Howson and Howson, Spring House Corporate Center, P.O. Box 457, Spring House, PA 19477 (US).	(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: METHOD OF MODIFYING CYTOTOXIC CELLS AND USES THEREOF		
(57) Abstract		
<p>TALL-104 cells, and other cytotoxic T cell lines, may be modified to increase the cytotoxicity thereof, to enhance growth properties, and/or to provide a preferred phenotype, e.g., expression of cell surface antigens, function, e.g., change in cytokine production profile, by culturing the cells in an effective amount of IL-15, optionally followed by gamma irradiation to halt proliferation.</p>		
Express Mail No. ET033647367US		

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FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
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AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
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CZ	Czech Republic	LJ	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

The demand must be filed directly with the International Preliminary Examining Authority or, if more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/US

PCT/PCT Rec'd 21 AUG 2001

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only			
Identification of IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference WST88PCT	
International application No. PCT/US00/04548	International filing date (day/month/year) 23 February 2000	(Earliest) Priority date (day/month/year) 24 February 1999	
Title of invention METHOD OF MODIFYING CYTOTOXIC CELLS AND USES THEREOF			
Box No. II APPLICANT(S)			
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) The Wistar Institute of Anatomy & Biology 3601 Spruce Street Philadelphia, Pennsylvania 19104-4268 United States		Telephone No.: 215-898-3763	
		Facsimile No.: 215-573-2456	
		Teleprinter No.:	
State (that is, country) of nationality: United States		State (that is, country) of residence: United States	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Santoli, Daniela 933 Wootton Road Bryn Mawr, Pennsylvania 19010 United States			
State (that is, country) of nationality: United States		State (that is, country) of residence: United States	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) Rovera, Giovanni 933 Wootton Road Bryn Mawr, Pennsylvania 19010 United States			
State (that is, country) of nationality: United States		State (that is, country) of residence: United States	
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Cesano, Alessandra
 226 W. Rittenhouse Square
 The Dorchester #413
 Philadelphia, Pennsylvania 19103
 United States

State (that is, country) of nationality:

Italy

State (that is, country) of residence:

United States

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:



Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCEThe following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Bak, Mary E.
Howson and Howson
Spring House Corporate Center
P.O. Box 457
Spring House, Pennsylvania 19477
United States

Telephone No.:

215-540-9200

Facsimile No.:

215-540-5818

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:***

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.**Box No. V ELECTION OF STATES**The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

received not received

- | | |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet | 4. <input type="checkbox"/> statement explaining lack of signature |
| 2. <input type="checkbox"/> separate signed power of attorney | 5. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other (specify): |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

By: Mary E. Bak
Mary E. Bak
Attorney for Applicants

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

INTERNATIONAL SEARCH REPORT

National application No.

PCT/US00/04548

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 5/00, 5/02

US CL : 435/375, 377; 530/351

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/375, 377; 530/351

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,820,856 A (SANTOLI ET AL) 13 October 1998(13.10.98), see entire document.	1-21
A	US 5,702,702 A (SANTOLI ET AL) 30 December 1997(30.12.97), see entire document.	1-21
A	US 5,683,690 A (SANTOLI ET AL) 04 November 1997(04.11.97), see entire document.	1-21
A	WO 94/26284 A1 (THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY) 24 November 1994(24.11.94), see entire document, especially claims 1 and 2.	1-21

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

19 APRIL 2000

Date of mailing of the international search report

27 JUL 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

MARIANNE DIBRINO

Facsimile No. (703) 305-3230

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04548

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GAMERO et al. Interleukin 15 Induction of Lymphokine-activated Killer Cell Function against Autologous Tumor Cells in Melanoma Patient Lymphocytes by a CD18-Dependent, Perforin-related Mechanism. Cancer Research. 01 November 1995, Vol. 55, pages 4988-4994, especially Abstract and Introduction.	1-21
A	CESANO et al. TWO UNIQUE HUMAN LEUKEMIC T-CELL LINES ENDOWED WITH A STABLE CYTOTOXIC FUNCTION AND A DIFFERENT SPECTRUM OF TARGET REACTIVITY ANALYSIS AND MODULATION OF THEIR LYTIC MECHANISMS. In Vitro Cell. Dev. Biol. September-October 1992, Vol. 28A, pages 648-656, especially Summary, Introduction and Materials and Methods.	1-21
A	CESANO et al. Effects of lethal irradiation and cyclosporin A treatment on the growth and tumoricidal activity of a T cell clone potentially useful in cancer therapy. Cancer Immunol Immunother. 1995, Vol. 40, pages 139-151, especially Abstract.	1-21
A	SANTOLI et al. SYNERGISTIC AND ANTAGONISTIC EFFECTS OF IL-1a AND IL-4, RESPECTIVELY, ON THE IL-2-DEPENDENT GROWTH OF A T CELL RECEPTOR-gd+ HUMAN T LEUKEMIA CELL LINE. The Journal of Immunology. 15 June 1990, Vol. 144, No. 12, pages 4703-4711, especially Abstract.	1-21
A	DISANTO. Cytokines: Shared receptors, distinct functions. Current Biology. 01 July 1997, Vol. 7, No. 7, pages R424-R426, see entire article.	1-21

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/04548

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

WEST 1.2, STN(MEDLINE, EMBASE, BIOSIS, CAPLUS, SCISEARCH)

search terms: culture, IL-15, IL-2, interleukin(s), Santoli, Daniela Cesano, Alessandra, CTL, cytotoxic T lymphocyte(s), TALL-104, TALL-103, CD38, IL-10, GM-CSF, TNF, CD56, differentiation, phenotype, cytokine(s)

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT/PT Rec'd 21 AUG 2001

PCT

WRITTEN OPINION

(PCT Rule 66)

To: MARY E. BAK
HOWSON AND HOWSON
SPRING HOUSE CORPORATE CENTER
P.O. BOX 457
SPRING HOUSE, PA 19477

RECEIVED
FEB 23 2001
RESOLUTIVE

Date of Mailing
(day/month/year)

22 FEB 2001

Applicant's or agent's file reference

WST88PCT

REPLY DUE

within TWO months
from the above date of mailing

International application No.

PCT/US00/04548

International filing date (day/month/year)

23 FEBRUARY 2000

Priority date (day/month/year)

24 FEBRUARY 1999

International Patent Classification (IPC) or both national classification and IPC
IPC(7): C12N 5/00, 5/02 and US Cl.: 435/375, 377; 530/351

ENTERED

Applicant

THE WISTART INSTITUTE OF ANATOMY AND BIOLOGY

DUE 4-22-01

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 24 JUNE 2001

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

Marianne Dibrino
MARIANNE DIBRINO

Telephone No. (703) 308-0196

WRITTEN OPINION

International application No.

PCT/US00/04548

I. Basis of the opinion

1. With regard to the **elements** of the international application: *

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-17 , as originally filed
 pages NONE , filed with the demand
 pages NONE , filed with the letter of _____
- ☒ the claims:
 pages 18-21 , as originally filed
 pages NONE , as amended (together with any statement) under Article 19
 pages NONE , filed with the demand
 pages NONE , filed with the letter of _____
- ☒ the drawings:
 pages 1-16 , as originally filed
 pages NONE , filed with the demand
 pages NONE , filed with the letter of _____
- ☒ the sequence listing part of the description:
 pages NONE , as originally filed
 pages NONE , filed with the demand
 pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
 These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacer¹ sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".

WRITTEN OPINION

International application No.

PCT/US00/04548

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims <u>1-21</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-21</u>	NO
Industrial Applicability (IA)	Claims <u>1-21</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations

Claims 1-21 lack an inventive step under PCT Article 33(3) as being obvious over Cesano et al (Cancer Immunol. Immunother. Vol. 40, hereafter "Cesano '40") in view of Cesano (In Vitro Cell Dev. Biol. Vol. 28A, hereafter "Cesano '28A"), Gamero et al, DiSanto and U.S. Patent No. 5,820,856.

Cesano '40 teaches that lethally irradiated TALL-104 cells require multiple cytokine stimulation for optimal expression of tumoricidal activity, and requires IL-2 for maintenance in culture (especially Abstract). Cesano '40 does not teach a method of modifying cytotoxic T cells comprising stimulation of said cells by culture in IL-15 and IL-2 (in any order) and the resulting cells after culture. Cesano '28A teaches TALL-103 and TALL-104 cells require exposure to IL-2 for maintenance of cytotoxic activity (especially page 648). Gamero teaches that IL-15 induces CTL and LAK cell activity and may enhance an antitumor response by these cell types. DiSanto teaches that IL-2 and IL-15 are both essential for the maintenance of lymphoid cells, IL-2 being required for homeostasis of thymic derived T cells and IL-15 being relevant for extrathymic lymphocyte development (especially page R426). U.S. Patent No. 5,820,856 discloses modification of TALL-104 cells using two interleukins, including IL-2, in the direction of increased cytotoxicity. The '856 patent also discloses the usefulness of the TALL-104 cells in adoptive immunotherapy (especially columns 11 and 12). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included or substituted IL-15 in the method of the '856 for the second lymphokine in order to enhance the cytotoxicity (as taught by Gamero) of the TALL-103 or TALL-104 cells for adoptive immunotherapy against tumors (as taught by '856 patent. The properties of the said modified cells recited in the claims are expected properties, and the reference cells are the same absent a showing to the contrary.

----- NEW CITATIONS -----
NONE

WRITTEN OPINION

International application No.

PCT/US00/04548

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: MARY E. BAK
HOWSON AND HOWSON
SPRING HOUSE CORPORATE CENTER
P.O. BOX 457
SPRING HOUSE, PA 19477

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing
(day/month/year) **20 JUN 2001**

Applicant's or agent's file reference

WST88PCT

IMPORTANT NOTIFICATION

International application No.

PCT/US00/04548

International filing date (day/month/year)

23 FEBRUARY 2000

Priority Date (day/month/year)

24 FEBRUARY 1999

Applicant

THE WISTART INSTITUTE OF ANATOMY AND BIOLOGY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US
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Washington, D.C. 20231

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Authorized officer

MARIANNE DIERINO

Telephone No. (703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference WST88PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/04548	International filing date (day/month/year) 23 FEBRUARY 2000	Priority date (day/month/year) 24 FEBRUARY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): C12N 5/00, 5/02 and US Cl.: 435/375, 377; 530/351		
Applicant THE WISTART INSTITUTE OF ANATOMY AND BIOLOGY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 3 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 20 SEPTEMBER 2000	Date of completion of this report 17 MAY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer  MARIANNE DIBRINO
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0196

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/04548

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed☒ the description:

pages 1-17, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the claims:

pages 18-21, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the drawings:

pages 1-16, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

☒ the sequence listing part of the description:

pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages NONE☒ the claims, Nos. NONE☒ the drawings, sheets/fig. NONE**5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/04548

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>1-21</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-21</u>	NO
Industrial Applicability (IA)	Claims <u>1-21</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-21 lack an inventive step under PCT Article 33(3) as being obvious over Cesano et al (Cancer Immunol. Immunother. Vol. 40, hereafter "Cesano '40") in view of Cesano (In Vitro Cell Dev. Biol. Vol. 28A, hereafter "Cesano '28A"), Gamero et al, DiSanto and U.S. Patent No. 5,820,856.

Cesano '40 teaches that lethally irradiated TALL-104 cells require multiple cytokine stimulation for optimal expression of tumoricidal activity, and requires IL-2 for maintenance in culture (especially Abstract). Cesano '40 does not teach a method of modifying cytotoxic T cells comprising stimulation of said cells by culture in IL-15 and IL-2 (in any order) and the resulting cells after culture. Cesano '28A teaches TALL-103 and TALL-104 cells require exposure to IL-2 for maintenance of cytotoxic activity (especially page 648). Gamero teaches that IL-15 induces CTL and LAK cell activity and may enhance an antitumor response by these cell types. DiSanto teaches that IL-2 and IL-15 are both essential for the maintenance of lymphoid cells, IL-2 being required for homeostasis of thymic derived T cells and IL-15 being relevant for extrathymic lymphocyte development (especially page R426). U.S. Patent No. 5,820,856 discloses modification of TALL-104 cells using two interleukins, including IL-2, in the direction of increased cytotoxicity. The '856 patent also discloses the usefulness of the TALL-104 cells in adoptive immunotherapy (especially columns 11 and 12). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included or substituted IL-15 in the method of the '856 for the second lymphokine in order to enhance the cytotoxicity (as taught by Gamero) of the TALL-103 or TALL-104 cells for adoptive immunotherapy against tumors (as taught by '856 patent. The properties of the said modified cells recited in the claims are expected properties, and the reference cells are the same absent a showing to the contrary.

----- NEW CITATIONS -----
NONE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

RECD 26 JUN 2001

WIPO PCT

Applicant's or agent's file reference WST88PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/04548	International filing date (day/month/year) 23 FEBRUARY 2000	Priority date (day/month/year) 24 FEBRUARY 1999
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Date of submission of the demand 20 SEPTEMBER 2000	Date of completion of this report 17 MAY 2001
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

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- ☒ the international application as originally filed
- ☒ the description:
pages 1-17, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the claims:
pages 18-21, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the drawings:
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pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages NONE
- ☒ the claims, Nos. NONE
- ☒ the drawings, sheets/fig NONE

5. ☐ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

**Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/US00/04548

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. statement**

Novelty (N)	Claims <u>1-21</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>NONE</u>	YES
	Claims <u>1-21</u>	NO
Industrial Applicability (IA)	Claims <u>1-21</u>	YES
	Claims <u>NONE</u>	NO

2. citations and explanations (Rule 70.7)

Claims 1-21 lack an inventive step under PCT Article 33(3) as being obvious over Cesano et al (Cancer Immunol. Immunother. Vol. 40, hereafter "Cesano '40") in view of Cesano (In Vitro Cell Dev. Biol. Vol. 28A, hereafter "Cesano '28A"), Gamero et al, DiSanto and U.S. Patent No. 5,820,856.

Cesano '40 teaches that lethally irradiated TALL-104 cells require multiple cytokine stimulation for optimal expression of tumoricidal activity, and requires IL-2 for maintenance in culture (especially Abstract). Cesano '40 does not teach a method of modifying cytotoxic T cells comprising stimulation of said cells by culture in IL-15 and IL-2 (in any order) and the resulting cells after culture. Cesano '28A teaches TALL-103 and TALL-104 cells require exposure to IL-2 for maintenance of cytotoxic activity (especially page 648). Gamero teaches that IL-15 induces CTL and LAK cell activity and may enhance an antitumor response by these cell types. DiSanto teaches that IL-2 and IL-15 are both essential for the maintenance of lymphoid cells, IL-2 being required for homeostasis of thymic derived T cells and IL-15 being relevant for extrathymic lymphocyte development (especially page R426). U.S. Patent No. 5,820,856 discloses modification of TALL-104 cells using two interleukins, including IL-2, in the direction of increased cytotoxicity. The '856 patent also discloses the usefulness of the TALL-104 cells in adoptive immunotherapy (especially columns 11 and 12). It would have been obvious to one of ordinary skill in the art at the time the invention was made to have included or substituted IL-15 in the method of the '856 for the second lymphokine in order to enhance the cytotoxicity (as taught by Gamero) of the TALL-103 or TALL-104 cells for adoptive immunotherapy against tumors (as taught by '856 patent). The properties of the said modified cells recited in the claims are expected properties, and the reference cells are the same absent a showing to the contrary.

----- NEW CITATIONS -----

NONE

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) WST88PCT

Box No. I TITLE OF INVENTION	
METHOD OF MODIFYING CYTOTOXIC CELLS AND USES THEREOF	
Box No. II APPLICANT	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
The Wistar Institute of Anatomy and Biology 3601 Spruce Street Philadelphia, Pennsylvania 19104-4268 United States of America	
<input type="checkbox"/> This person is also inventor.	
Telephone No. 215-898-3763	
Facsimile No. 215-573-2456	
Teleprinter No.	
State (that is, country) of nationality: United States of America	State (that is, country) of residence: United States of America
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)	
Santoli, Daniela 933 Wootton Road Bryn Mawr, Pennsylvania 19010 United States of America	
This person is: <input type="checkbox"/> applicant only <input checked="" type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)	
State (that is, country) of nationality: United States of America	State (that is, country) of residence: United States of America
This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box	
<input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)	
Bak, Mary E. Howson and Howson Spring House Corporate Center P.O. Box 457 Spring House, Pennsylvania 19477 United States of America	
Telephone No. 215-540-9200	
Facsimile No. 215-540-5818	
Teleprinter No.	
<input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Rovera, Giovanni
933 Wootton Road
Bryn Mawr, Pennsylvania 19010
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
United States of America

State (that is, country) of residence:
United States of America

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

Cesano, Alessandra
226 W. Rittenhouse Square
The Dorchester, #413
Philadelphia, Pennsylvania 19103
United States of America

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
Italy

State (that is, country) of residence:
United States of America

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☐ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|--|--|
| <input type="checkbox"/> AE United Arab Emirates | <input type="checkbox"/> LR Liberia |
| <input type="checkbox"/> AL Albania | <input type="checkbox"/> LS Lesotho |
| <input type="checkbox"/> AM Armenia | <input type="checkbox"/> LT Lithuania |
| <input type="checkbox"/> AT Austria | <input type="checkbox"/> LU Luxembourg |
| <input checked="" type="checkbox"/> AU Australia | <input type="checkbox"/> LV Latvia |
| <input type="checkbox"/> AZ Azerbaijan | <input type="checkbox"/> MA Morocco |
| <input type="checkbox"/> BA Bosnia and Herzegovina | <input type="checkbox"/> MD Republic of Moldova |
| <input type="checkbox"/> BB Barbados | <input type="checkbox"/> MG Madagascar |
| <input type="checkbox"/> BG Bulgaria | <input type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input type="checkbox"/> BR Brazil | |
| <input type="checkbox"/> BY Belarus | <input type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> CA Canada | <input type="checkbox"/> MW Malawi |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input type="checkbox"/> MX Mexico |
| <input type="checkbox"/> CN China | <input type="checkbox"/> NO Norway |
| <input type="checkbox"/> CR Costa Rica | <input type="checkbox"/> NZ New Zealand |
| <input type="checkbox"/> CU Cuba | <input type="checkbox"/> PL Poland |
| <input type="checkbox"/> CZ Czech Republic | <input type="checkbox"/> PT Portugal |
| <input type="checkbox"/> DE Germany | <input type="checkbox"/> RO Romania |
| <input type="checkbox"/> DK Denmark | <input type="checkbox"/> RU Russian Federation |
| <input type="checkbox"/> DM Dominica | <input type="checkbox"/> SD Sudan |
| <input type="checkbox"/> EE Estonia | <input type="checkbox"/> SE Sweden |
| <input type="checkbox"/> ES Spain | <input type="checkbox"/> SG Singapore |
| <input type="checkbox"/> FI Finland | <input type="checkbox"/> SI Slovenia |
| <input type="checkbox"/> GB United Kingdom | <input type="checkbox"/> SK Slovakia |
| <input type="checkbox"/> GD Grenada | <input type="checkbox"/> SL Sierra Leone |
| <input type="checkbox"/> GE Georgia | <input type="checkbox"/> TJ Tajikistan |
| <input type="checkbox"/> GH Ghana | <input type="checkbox"/> TM Turkmenistan |
| <input type="checkbox"/> GM Gambia | <input type="checkbox"/> TR Turkey |
| <input type="checkbox"/> HR Croatia | <input type="checkbox"/> TT Trinidad and Tobago |
| <input type="checkbox"/> HU Hungary | <input type="checkbox"/> TZ United Republic of Tanzania |
| <input type="checkbox"/> ID Indonesia | <input type="checkbox"/> UA Ukraine |
| <input type="checkbox"/> IL Israel | <input type="checkbox"/> UG Uganda |
| <input type="checkbox"/> IN India | <input checked="" type="checkbox"/> US United States of America |
| <input type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input type="checkbox"/> UZ Uzbekistan |
| <input type="checkbox"/> KE Kenya | <input type="checkbox"/> VN Viet Nam |
| <input type="checkbox"/> KG Kyrgyzstan | <input type="checkbox"/> YU Yugoslavia |
| <input type="checkbox"/> KP Democratic People's Republic of Korea | <input type="checkbox"/> ZA South Africa |
| | <input type="checkbox"/> ZW Zimbabwe |

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐
- ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Supplemental Box*If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
 - (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
 - (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
 - (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
 - (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
 - (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
 - (vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.
2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.
3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

"Continuation of Box No. IV"

Kita, Stanley B.
 Smith, George A., Jr.
 Kodroff, Cathy A.
 Bak, William

All above attorneys are members of the firm of Howson and Howson.
 Address of all is indicated in Box IV.

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 24 February 1999	60/121,482	United States		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / US

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 5

description (excluding sequence listing part) : 16

claims : 4

abstract : 1

drawings : 16

sequence listing part of description : _____

Total number of sheets : 42

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney, reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☒ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): transmittal letter to the USRO

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

By:

Mary E. Bak

Attorney for Applicants

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Applicant's or agent's file reference number	WST88PCT	International application No.
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

A. The indications made below relate to the microorganism referred to in the description on page <u>10</u> , line <u>2</u>	
B. IDENTIFICATION OF DEPOSIT <u>TALL-104 cell lines</u> Further deposits are identified on an additional sheet <input type="checkbox"/>	
Name of depositary institution <u>American Type Culture Collection</u>	
Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209 USA</u>	
Date of deposit <u>June 15, 1998</u>	Accession Number <u>CRL 11386</u>
C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/>	
D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States)	
E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable)	
The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit")	

For receiving Office use only
<input type="checkbox"/> This sheet was received with the international application
Authorized officer

For International Bureau use only
<input type="checkbox"/> This sheet was received by the International Bureau on:
Authorized officer